

Fetal alcohol syndrome and the developing socio-emotional brain

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Abstract

Fetal alcohol syndrome (FAS) is currently recognized as the most common known cause of mental retardation, affecting from 1 to 7 per 1000 live-born infants. Individuals with FAS suffer from changes in brain structure, cognitive impairments, and behavior problems. Researchers investigating neuropsychological functioning have identified deficits in learning, memory, executive functioning, hyperactivity, impulsivity, and poor communication and social skills in individuals with FAS and fetal alcohol effects (FAE). Investigators using autopsy and brain imaging methods have identified microcephaly and structural abnormalities in various regions of the brain (including the basal ganglia, corpus callosum, cerebellum, and hippocampus) that may account for the neuropsychological deficits. Results of studies using newer brain imaging and analytic techniques have indicated specific alterations (i.e., displacements in the corpus callosum, increased gray matter density in the perisylvian regions, altered gray matter asymmetry, and disproportionate reductions in the frontal lobes) in the brains of individuals prenatally exposed to alcohol, and their relations with brain function. Future research, including using animal models, could help inform our knowledge of brain-behavior relations in the context of prenatal alcohol exposure, and assist with early identification and intervention.

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1. Introduction

A reference to the adverse effects of alcohol on the fetus can be found as far back as the Old Testament: “Beware, and drink no wine or strong drink . . . for lo, you shall conceive and bear a son” (Judges 13:4, 5). The first scientific study addressing the risk of drinking during pregnancy was conducted in 1899, and found an increased rate of still-birth and infant death in children of alcoholic women (Sullivan, 1899). In the 1940s, scientists concluded that the developmental abnormalities of children born to alcoholic mothers were secondary to the environment in which they were raised (e.g., Haggard & Jellinek, 1942). During the next two decades, several French reports described the children of alcoholic mothers as having malformations, growth deficiency, and psychomotor disturbances (Lamache, 1967; Lemoine, Harousseau, Borteryu, & Menuet, 1968), but

these reports did not achieve general recognition. In the early 1970s, interest in the adverse effects of alcohol on fetal development was revived, and awareness of alcohol as a teratogen was raised. Growth deficiency and developmental delay were documented in the children of chronically alcoholic women (e.g., Ulleland, 1972). A landmark report described eight unrelated children of three different ethnic groups, all born to mothers who were chronic alcoholics, as having a characteristic “pattern of malformation” (Jones, Smith, Ulleland, & Streissguth, 1973) and the term fetal alcohol syndrome (FAS) was introduced shortly thereafter (Jones & Smith, 1973).

Over the past 30 years, the risks and consequences of consuming alcohol during pregnancy have been reported by hundreds of investigators throughout the world. Clinical reports have been supplemented by experimental studies of animals. The evidence clearly implicates alcohol as a teratogen (e.g., Abel, 1990). This paper is a follow-up to a literature review published over 10 years ago (Niccols, 1994). Since that time, neuroscience methodology has

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advanced a great deal, permitting the application of new methods to further our understanding of FAS and its impact on brain structure and function. The purpose of this paper is to provide an updated review, highlighting the results of studies of the neuropsychological characteristics and brain structure of individuals with FAS, as well as the recent research on connections between neurological structure and function in individuals with FAS.

2. Diagnosis and classification

FAS is defined as a concurrent triad of signs consisting of characteristic facial dysmorphism, prenatal and postnatal growth deficiency, and central nervous system dysfunction (Jones & Smith, 1973; Sokol & Clarren, 1989). Dysmorphic facial features include short palpebral fissures, an elongated mid-face, long and flat philtrum, thin upper vermilion, flattened maxilla, and hypoplasia of the nasal bridge (Clarren & Smith, 1978; Jones & Smith, 1973; Sokol & Clarren, 1989). A 10-year follow-up study provided some evidence that the craniofacial malformations that are characteristics of FAS may diminish over time (Spohr, Willms, & Steinhausen, 1993). The growth deficiency of FAS usually begins prenatally and is characterized by postnatal weight and/or length or height below the 10th percentile for age or gestational age (Sokol & Clarren, 1989). Although some long-term compensatory growth has been observed and body weight may normalize by adolescence in females with FAS (Spohr et al., 1993), the growth parameters of many individuals with FAS are well below the 3rd percentile in childhood and remain this low through adolescence and adulthood (e.g., Streissguth, Clarren, & Jones, 1985). Head circumference is characteristically below the 3rd percentile (e.g., Sokol & Clarren, 1989). Central nervous system dysfunction continues to be one of the most detrimental effects of prenatal alcohol exposure, with structural and functional brain damage (Streissguth, 1997). In studies of intellectual functioning, children with FAS have demonstrated an average IQ of between 60 and 65, with a wide range of individual IQ scores (Streissguth et al., 1994). Other physiological features of FAS include cleft palate and possibly other organ or organ system damage such as heart, kidney, and/or vision defects (e.g., Burd & Martsolf, 1989).

It has become apparent that alcohol, like other teratogens, gives rise to a spectrum of defects, with affected children showing much individual variation in both the extent and severity of their involvement. At the less severely affected end of the continuum, for example, Shaywitz, Cohen, and Shaywitz (1980) have reported varying degrees of facial dysmorphism, growth deficiencies, attention problems, and learning difficulties in children of normal intelligence born to alcoholic mothers. This finding is not surprising, because other birth defects also confer varying degrees of impairment on those affected. The term “fetal alcohol syndrome” refers to individuals on the more severely affected end of the continuum where the complete

triad of facial dysmorphism, growth deficiency, and mental retardation is expressed. The present article is concerned primarily with these individuals. Other terms, such as “fetal alcohol effects” (FAE) and “prenatal alcohol exposed” have been used to describe children who show less extreme examples of difficulties following prenatal alcohol exposure, and the umbrella term “fetal alcohol spectrum disorder” (FASD) is used to describe the full range of outcomes observed among individuals with prenatal alcohol exposure. Where available, information pertaining to individuals with FAE and prenatal alcohol exposure will be reported using this terminology.

2.1. Etiology

FAS is caused by heavy maternal alcohol consumption during pregnancy. Numerous controlled experimental studies with animals have demonstrated the teratogenicity of alcohol (for a review, see Abel, 1990). Ethanol freely crosses the placenta, thus directly affecting developing fetal cells and tissues.

2.1.1. Mechanisms

The mechanisms by which ethanol may damage the developing central nervous system differ depending on the stage of embryological development (Pratt, 1984; Riley & McGee, 2005). At the time of conception and during the first weeks of prenatal development, ethanol may act as a cytotoxic or mutagenic agent, causing either cell death or lethal chromosomal aberrations. Evidence of this comes from experiments examining the effect of ethanol on embryonic tissue culture (e.g., Cook, Keiner, & Yen, 1990) and from the high rate of miscarriage in alcoholics (e.g., Olegard et al., 1979).

During the period roughly 4 to 10 weeks after conception, ethanol can act cytotoxically, causing excessive cell death in the central nervous system and abnormalities in nerve cell migration from cell damage. From the changes described in postmortem studies of FAS (e.g., Clarren, Alvord, Sumi, Streissguth, & Smith, 1978), evidence indicates that abnormal migration leads to disorganization of tissue structure, and severe cell loss leads to microcephaly. A similar pattern of brain damage is reproducible in mice given a suitably timed dose of ethanol (e.g., Miller, 1993, 1996). Early shortening of the anterior cranial base due to an alcohol-induced deficiency in brain growth explains the changed shape of the mid-face that makes FAS recognizable (Kotch & Sulik, 1992).

Later in pregnancy, from 8 to 10 weeks onwards, ethanol can again disorganize or delay cell migration and development (Pratt, 1984). If nerve cells are not in the right place at the right time, synapses will not be formed normally (Volk et al., 1981). In the third trimester, alcohol exposure is associated with damage to the cerebellum, hippocampus, and prefrontal cortex (e.g., Livy, Miller, Maier, & West, 2003; West & Pierce, 1986). Such biological mal-

formation may underlie the behavioral problems and neurological deficits of children with FASD.

Some researchers suggest that the neurological problems of individuals with FAS may be a result of perinatal hypoxia and acidosis secondary to ethanol-related impairment of umbilical circulation (e.g., Randall, Ekblad, & Anton, 1990). Throughout pregnancy, impaired placental transport of essential nutrients also may be involved (e.g., Fisher et al., 1983).

Also, alcohol interferes in various ways with neurotransmitter production in the central nervous system, leading to neuroendocrine abnormalities. These abnormalities include an effect on the hypothalamus that leads to suppression of growth hormone release (Thadani & Schanberg, 1979). The growth hormone deficiency thus produced may account for the growth deficit (probably including brain growth), which is the most consistent finding in the infants of alcoholic mothers. Alcohol consumption increases maternal and fetal hypothalamic-pituitary-adrenal (HPA) activity, and can disrupt hormonal interactions between maternal and fetal systems, affecting the development of fetal metabolic, physiologic, and endocrine functions (Zhang, Sliwowska, & Weinberg, 2005). Recent research suggests that ethanol interferes with neurotransmitter mechanisms, thereby disrupting synaptogenesis and causing neurons to commit suicide (die by apoptosis) on a massive scale (Olney, 2004).

Still to be determined is whether ethanol acts directly through an accumulation of its highly toxic first metabolite, acetaldehyde, or both (Pratt, 1984; Randall et al., 1990). Nevertheless, it is important to note that damage by several of the suggested mechanisms could occur before a woman even has known that she is pregnant.

2.1.2. Risk factors

Not all children of alcoholic mothers are born with FAS (Clarren, 1988). In fact, the effects of heavy maternal alcohol consumption on the fetus range from no damage to fetal death. The probability of a child whose mother drank heavily during pregnancy having FAS ranges from 1% to approximately 50% (Burd & Martsolf, 1989; Clarren, 1988). For example, in the Cleveland prospective study of over 12,000 women, Sokol, Miller, and Reed (1980) identified 204 “alcoholics.” Of these 204 women, only 5 gave birth to babies with FAS. Why some children born to alcoholic women have FAS and others do not is an enigma.

To assess risk factors, Abel (1983) tabulated information from over 300 clinical case studies of FAS. Stage of maternal alcoholism and parity were considered risk factors because women in the chronic phase of alcoholism were more likely to produce children with FAS than those in the early stage of alcoholism, and later born children were at higher risk than firstborns. More recent research also has implicated maternal age as an important risk factor, with infants of older mothers (over 30) at more risk than those of younger mothers (e.g., Jacobson, Jacobson, Sokol, Chiodo, & Corobana, 2004). Other research has

shown that the risk to the fetus also depends on the amount of alcohol consumed, the period of gestation during which the embryo was exposed, the pattern of consumption (binge vs. steady), and maternal and fetal metabolism (see Abel, 1990, for a review). Poor nutritional status, multiple drug use, poverty, physical stress, obstetric complications, obstetric medication, fetal tissue sensitivity, genetic susceptibility, and paternal alcohol consumption, as well as their interactions, and unknown factors also may increase the risk of FAS in pregnant alcoholics.

2.2. Prevalence and incidence

FAS is the most common identifiable cause of mental retardation and occurs more often than the two most common birth defects (Down syndrome and spina bifida) combined (National Institute on Alcohol Abuse & Alcoholism, 1990). Prevalence estimates for FAS range from 1 to 7 per 1000 live births (Abel, 1995; Clarren, Randels, Sanderson, & Fineman, 2001; May et al., 2006; Sampson et al., 1997), although rates for FASD as high as 10 to 40 per 1000 have been found (May et al., 2006; Sampson et al., 1997). Estimates of the prevalence of FAS among chronically alcoholic women are 25 per 1000 (Abel, 1988), which is higher than most population estimates. Prospective studies suggest that FAS is grossly under-diagnosed and under-reported (e.g., Abel & Sokol, 1987; Clarren et al., 2001).

2.3. Psychological characteristics

When considering research findings in the area of psychological characteristics of individuals with FAS, it is important to keep in mind that, because children with FAS are usually raised in foster homes or in homes where one or both parents are alcoholic, a variety of additional risks to development may be present. It is probable that, as is the case with typically developing children, variability in postnatal environment contributes to variability in mental development, behavior, and general adjustment in children with FAS.

2.3.1. Early development

Jacobson, Jacobson, Behun, Chiodo, and Sokol (1999) found high basal and post-stress cortisol levels in infants of mothers who reported high levels of drinking during pregnancy. Fetal programming of HPA activity may result in hyper-responsiveness to stress and immune system vulnerability (Zhang et al., 2005). Infant rats and humans with FAS or FAE show high levels of irritability and feeding and sleeping difficulties (e.g., Kelly, Day, & Streissguth, 2000; Streissguth & Giunta, 1988). As preschoolers, the “signals” of FAS include “short, skinny children with butterflylike movements who are hyperactive and/or excessively friendly and fearless” (Streissguth & Giunta, 1988). Hyperactivity, language delay, articulation problems, poor motor coordination, and developmental delay are often noted during this period (e.g., Clarren, 1988; Steinhausen,

Nestler, & Spohr, 1982). Health concerns often include infections (e.g., Johnson, Knight, Marmer, & Steele, 1981), dental anomalies (Streissguth et al., 1985), ocular anomalies (Stromland, 1985), and otitis media (e.g., Streissguth et al., 1985).

2.3.2. Intellectual ability

Studies have shown that IQ scores for the majority of infants, children, and adults with FAS are between 40 and 80, with a mean of 60 to 65; however, psychometric test findings vary depending on the study sample and tests used (e.g., Jones & Smith, 1973; Streissguth et al., 1994). Further, there is a wide range of individual differences, with reported IQ scores ranging from 16 to 120 (Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998; Streissguth, Barr, Sampson, Darby, & Martin, 1978; Streissguth, Randels, & Smith, 1991). The existence of average range IQ in children with FAS suggests that there will be exceptions to the prediction of mental retardation on the basis of a diagnosis of FAS in infancy. The distinction between FAS and FAE is often difficult to make because of the blurred (and artificial) boundary between these diagnoses. Follow-up studies indicate that IQ scores for individuals with FAS remain quite stable from early childhood to adolescence and adulthood (e.g., Streissguth et al., 1991).

A continuing controversy in the assessment of cognitive functioning in children with FAS involves the degree to which the deficits derive from prenatal alcohol exposure rather than from neglectful and/or nonstimulating environments often provided by alcoholic mothers who continue to drink. While this issue cannot be resolved definitively, it has been pointed out that some children with FAS have been raised entirely by excellent adoptive families and continue to exhibit developmental delay (e.g., Streissguth & LaDue, 1985).

2.3.3. Neuropsychological abilities

The neuropsychological impairments of individuals with FAS include deficits in memory, attention, motor skills, visual-spatial abilities, and learning (e.g., Olson et al., 1998; Riley & McGee, 2005). Individuals with FAS also exhibit deficits in executive functions thought to be mediated by the frontal lobe of the brain (Welsh, Pennington, & Grossier, 1991), such as cognitive flexibility, planning and strategy use, verbal reasoning, inhibition, set shifting, fluency, working memory, and emotion-related learning (Rasmussen, 2005). These difficulties exist in similar degree in individuals with FAE and FAS, regardless of facial characteristics, and are worse than predicted on the basis of IQ (e.g., Connor, Sampson, Bookstein, Carr, & Streissguth, 2000). Some inconsistent findings have been noted, as research in this area typically involves small samples, large age ranges, and inconsistent measurement tools (Rasmussen, 2005). Despite the difficulties inherent in identifying the core deficit in FAS, there is some evidence that it may be working memory (e.g., Rasmussen, 2005) or pro-

cessing speed (e.g., Burden, Jacobson, & Jacobson, 2005), although controversy continues (e.g., Kulaga, 2006).

2.3.4. Hearing, speech, and language

The craniofacial abnormalities of FAS (which sometimes include cleft palate) make children with FAS prone to otitis media with effusion and conductive hearing loss (Church & Kaltenbach, 1997). In an early study investigating speech and language problems in individuals with FAS, Iosub, Fuchs, Bingol, and Gromisch (1981) observed voice dysfunction, articulation disorders, fluency problems, and language impairment (the basis for which could not be associated with hearing deficits) in 80% of the 45 school-age children examined. Since then, others have confirmed speech and language delay in children with FAS compared to typically developing peers (e.g., Steinhausen et al., 1982). In their detailed study of the communication abilities of eight children with FAS, Becker, Warr-Leeper, and Leeper (1990) found more oral-motor deficits, articulation problems, and difficulties in the comprehension and use of grammatical markers, as well as a reduced capacity to process and store linguistic elements, than among controls matched for ethnic background, living situation, and non-verbal cognitive ability. The investigators emphasized that these language abilities were lower than would be expected given child IQ.

2.3.5. Social development

Atypical attachment behavior and impairments in state regulation are observed in both infant humans and rats prenatally exposed to alcohol (Kelly et al., 2000). Children with FAS have been described as outgoing, socially engaging, affectionate, and “excessively friendly” (Streissguth & Giunta, 1988). Preschoolers with FAS do not appear to differentiate familiar from unfamiliar persons, and seem to enjoy tactile social interactions and bodily contact (Streissguth & Giunta, 1988). Although endearing in young children with FAS, this type of social behavior raises concerns for their safety and behavior management as they develop. Studies involving parental and teacher reports on children, adolescents, and adults with FAS and FAE have identified particular difficulties with social skills, beyond that explained by IQ and suggesting arrested, not delayed, social development (e.g., Thomas, Kelly, Mattson, & Riley, 1998). The social impairments of individuals with FAS and FAE have been attributed to language difficulties and underlying impairments in cognitive and executive functioning, and some have speculated a deficit in “theory of mind” the ability to infer another’s perspective, especially when it differs from one’s own (e.g., Coggins, Olswang, Olson, & Timler, 2003). In rats, prenatal alcohol exposure results in changes in aggression, social interaction, social recognition and communication, maternal behavior, and sexual behavior (Kelly et al., 2000). Animal studies have provided important information suggesting that impairments in social development may be the result of prenatal alcohol exposure and not the postnatal environment.

2.3.6. Adaptive functioning

Although there is considerable variation in the daily living skills and abilities of individuals with FAS, studies indicate that, as a group, their adaptive skills are significantly impaired. Children and adolescents with FAS and FAE exhibit poor socialization and communication skills (worse than would be predicted from their IQ and demographic characteristics) and significant maladaptive behaviors (e.g., impulsivity) that seem to worsen with age, and, as adults, are not likely to be living independently (e.g., Streissguth et al., 1991; Whaley, O'Connor, & Gunderson, 2001).

2.3.7. Behavior problems and psychopathology

The behavioral disorder most frequently noted in clinical papers and research reports describing children with FAS is attention deficit hyperactivity disorder (e.g., Riley & McGee, 2005). During the preschool period, hyperactivity is present in 85% of children with FAS (Streissguth & Giunta, 1988). Children with FAS also have been found to exhibit more eating and sleeping problems, rocking, ticks, phobias, temper tantrums, enuresis, encopresis, and peer difficulties than controls matched on age, sex, socioeconomic status, and living situation (Steinhausen et al., 1982). Studies involving parental reports have identified disruptive behaviors that interfere with participation in home, school, and community environments (Mattson & Riley, 2000). In their examination of the life history of adults with FAS, Streissguth & Randels (1988) found a high incidence of psychosocial difficulties. Other studies have reported increased risk for psychiatric disorders, trouble with the law, alcohol and drug use, and other maladaptive behaviors in individuals with FAS and FAE (e.g., Schonfeld, Mattson, & Riley, 2005; Streissguth et al., 2004).

2.4. Brain structure

Researchers using autopsy and brain imaging methods have found reductions and abnormalities in brain size and shape, especially in structures such as the basal ganglia, corpus callosum, cerebellum, and hippocampus (Riley & McGee, 2005). Magnetic resonance imaging (MRI), functional MRI (fMRI), electroencephalography (EEG), positron emission tomography (PET), and single photon emission computed tomography (SPECT) have allowed for the examination of specific alterations in the brains of individuals with FASD, and their relations with brain function. In early studies, quantitative structural analyses were performed, and recent advances in image analysis have further refined knowledge of brain structure and function in the context of prenatal alcohol exposure.

2.4.1. Basal ganglia

MRI studies have demonstrated disproportionate reductions in basal ganglia volume in children with FAS and FAE, especially the caudate nucleus (e.g., Archibald

et al., 2001), which is thought to be involved in higher cognitive functions and, via neural connections to the frontal lobes, executive functioning. Clark et al.'s (2000) PET study revealed reduced metabolic activity in the caudate nucleus in high functioning adolescents and adults with FAS.

2.4.2. Corpus callosum

Autopsy and MRI studies have revealed abnormalities of the corpus callosum in individuals with FAS, including agenesis but more commonly thinning in the anterior and posterior regions (Riley et al., 1995; Sowell, Mattson et al., 2001). Displacement of the isthmus and splenium have been observed and related to deficits in verbal learning (i.e., the greater the displacement, the more impairment in performance; Sowell, Mattson et al., 2001).

2.4.3. Cerebellum

Investigators have demonstrated disproportionate reductions in cerebellar volume in FAS and FAE, specifically in the anterior vermis (e.g., Archibald et al., 2001). The cerebellum is involved in both motor skills (balance and coordination) and learning. Deficits in cerebellar processing have been associated with dyslexia (e.g., Coffin, Baroody, Schneider, & O'Neill, 2005).

2.4.4. Hippocampus

Animal research, both behavioral and neuroanatomical, associates the teratogenic effects of prenatal alcohol exposure with damage to the hippocampus (Berman & Hannigan, 2000). In a MRI study, Riikonen, Salonen, Partanen, & Verho (1999) demonstrated that children with FAS had smaller left hippocampus volume than right. This asymmetry was greater than is typical, and associated with memory deficits.

2.4.5. Other anomalies

Kaneko and colleagues (Kaneko, Phillips, Riley, & Ehler, 1996) documented atypical EEG readings in approximately 50% of the children and adolescents with FAS in their sample, specifically, reductions in the power of the left hemisphere alpha frequencies (suggesting immature brain activity), and prolonged latency in P300 spikes in the parietal cortex (suggesting deficits in information processing). Others have found disproportionate reductions in the parietal lobe, as well as relative increases in gray matter and decreases in white matter in the perisylvian cortices of the temporal and parietal lobes (Archibald et al., 2001; Malisz et al., 2005; Sowell, Thompson et al., 2001).

Reduced cortical surface gray matter asymmetry and left hemisphere abnormalities also have been observed in children with FASD (Sowell et al., 2002). In a SPECT study, Riikonen et al. (1999) found that children with FAS demonstrated similar metabolic activity in both hemispheres, rather than the typical asymmetry with greater left hemisphere activity found in typically developing children. These findings are consistent with Kanetko et al. (1996).

EEG findings, and may account for the language skill deficits observed in FAS.

Recent studies have demonstrated disproportionate reductions in the ventral portions of the frontal lobes (especially the left; Archibald et al., 2001; Malisza et al., 2005; Sowell, Thompson et al., 2001, 2002). In individuals with FAS, Riihonen et al. (1999) noted increased blood supply to the right frontal region, which is characteristic of children with attention deficit hyperactivity disorder and accompanying executive function deficits. Other researchers have linked prenatal alcohol exposure to abnormalities of the frontal cortex in rats (e.g., Mihalick, Crandall, Langois, Krienke, & Dube, 2001). Using fMRI, Connor & Mahurin (2001) found atypical prefrontal cortex activation in adults with FAS and FAE during a working memory task, suggesting that the task was more difficult for these individuals and required greater than expected involvement of this brain region.

3. Summary

The devastating effects of maternal alcoholism and intrauterine alcohol exposure on development have been documented by numerous studies. It is evident that brain and behavior are affected by FASD, and that research in this area can inform our knowledge of brain-behavior relations. Recent studies indicate that the impact of prenatal alcohol exposure seems to affect certain neuroanatomical areas and neuropsychological functions more than others. Future studies using animal models could help link specific brain structures to functions in the context of prenatal alcohol exposure, and would be especially informative.

Research on brain structure and behavioral phenotypes is critical to early identification of FASD, especially in situations where accurate maternal drinking history is unavailable. Without such research, the difficulties with under-diagnosis are likely to continue. Accurate, early diagnosis is important to early intervention with this population. Further, identification of the core deficits and brain structures involved might enable the identification of more effective, targeted early intervention strategies (e.g., neonatal MRI to measure corpus callosum angle, Bookstein et al., 2005; perinatal supplementation with choline to stimulate hippocampal activity and short-term memory, Thomas, Garrison, & O'Neill, 2004; inhibition of brain growth restriction with neuroprotective peptides, Sari & Gozes, 2006), and investigation of the impact of intervention on structure and function of the developing brain.

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